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Editorial

Biomaterials, Cells, and Patho-physiology: Building Better Organoids and On-Chip Technologies



Three-dimensional *ex vivo* cellular cultures, engineered through cellular self-assembly under natural extracellular matrix (ECM) cues or through a biomaterial-based directed assembly, have emerged as powerful *in vitro* technologies for a wide range of biomedical applications. The *ex vivo* tissue models imitate one or more physiologically-relevant features and functions of target organs. The on-chip technologies and materials-based organoids have garnered enormous momentum, in the past few years, for their applications in disease modeling, mammalian tissue development, drug screening, and therapy design or even organ replacement. This “Organoids on a Chip” special issue focuses on the *ex vivo* tissue constructs in a dish and on-chip format for a wide range of tissues and organ systems, including liver, heart, muscle, lung, musculoskeletal, and immune system. The special issue presents a collection of original research articles and review perspectives from experts in their respective fields.

In this issue, Milica Radisic and colleagues review recent advances in the engineering of functional *in vitro* tissue model systems for studying the pathophysiology of cardiovascular diseases and drug screening applications. They provide an overview of small and large *in vivo* animal models and discuss 3D *in vitro* tissue engineered as well as on-chip models for cardiovascular diseases research. Their article further discussed the opportunities of engineered *in vitro* tissue model systems for the discovery of novel therapeutic targets for the treatment of cardiovascular diseases. Nasim Annabi and colleagues review recent advancements in the development of smart biomaterials, biofabrication techniques, and stem cell engineering, aimed at recapitulating cardiovascular function at the tissue- and organ levels. They provide a perspective on the clinical relevance of the existing approaches and future development towards personalized targeted therapeutics.

In a research article, Claudia Fischbach and colleagues report the development of a 3D tissue system, using mineralized collagen-I hydrogel, to mimic collagen matrix in bone and to gain a better insight on the biological mechanisms of breast cancer bone metastasis. The outcome of this work demonstrated reduced cancer cell adhesion and alerted migration profile, highlighting the influence of mineralization of collagen matrix on the biological response of cancer cells through integrin-mediated mechanotransduction. Within the space of pathophysiological tumor models, Yanan Du and team report the development of a 3D micro-tumor array system for anti-cancer drug screening. The proposed high-density 3D micro-tumor model was established based on dispensing target cells into porous gelatin micro-scaffold within a 384-well system. They utilized primary cells from patient-derived xenografts (PDX) or patient biopsies to test the reliability of their platform in chemotherapeutic screening. Their findings demonstrated better recapitulation of *in vivo* drug efficacy, using the 3D micro-tumor array system, as compared to 2D conventional assays. Shyni Varghese and colleagues further review the recent developments in the synthesis of bioinspired materials for bone tissue engineering and

disease modeling applications. Their review article specifically highlights the use of bioinspired materials, such as calcium phosphate or collagen-based matrices, to mimic the biophysical and biochemical cues of the native bone environment. The article further discussed the engineering of organ-on-chip systems for recapitulation of bone pathologies and drug screening applications.

In this issue, in a research article, Ankur Singh and colleagues report the development of a designer hydrogel-based synthetic immune tissue (in a dish) that shows the ability to generate high-affinity antigen-specific antibody formation. They report a maleimide (MAL)-functionalized polyethylene glycol (PEG)-based designer immune tissues that modulate B cell differentiation and enriches antigen-specific germinal center B cells in the presence of T-cell like signals. The *ex vivo* antigen-specific platform technology offers its use in scientific understanding of immunobiology, matrix immunology, and in biotechnology applications, ranging from the antigen testing, vaccine development, and generation of antibodies against diseases. On the other hand, Thomas Webster and colleagues reviewed the recent developments of *in vitro* platform technologies and *ex vivo* systems for modeling of infectious diseases. In their article, they discuss the advantages and limitations of currently available biofilm model systems, 3D organoid, and microfluidic models, as well as *ex vivo* and *in vivo* models which have been utilized for infection studies. In a new research article, Roger Kamm and colleagues develop a 3D vascularized microfluidic model and provide evidence of direct engagement between human monocytes and tumor cells in a 3D vascularized microfluidic model. They report that inflammatory, but not patrolling, monocytes rely on actomyosin-based motility. This study brings important insight into the role of monocytes in cancer cell extravasation and sheds light on the metastatic cascade.

In a series of research and review articles, Christine Schmidt, Brendan Harley, and Mehdi Nikkhah describe *ex vivo* models of the brain system. Schmidt and colleagues provide an overview of the technologies related to *ex vivo* models and lab-on-a-chip devices for studying the regeneration of the brain, spinal cord, and peripheral nerve tissues. Importantly, they also review current commercial products that mimic diseased and normal neural tissues and discuss the future directions in this field. In a research article, Harley and colleagues describe how perivascular signals alter global gene expression profile of glioblastoma and response to temozolomide in a gelatin hydrogel-based tumor model. By combining the results of an engineered hydrogel and RNA sequencing, they further demonstrate the upregulation and downregulation of genes related to angiogenesis, DNA damage repair, extracellular matrix remodeling etc. under specific disease conditions and perivascular niche. Nikkhah and colleagues posit that glioma stem cell populations in glioblastoma are highly tumorigenic, invasive, and resistant to several forms of therapy. They developed a 3D organotypic microfluidic platform, integrated with hydrogel-based biomaterials, to mimic the glioma stem cell

vascular niche and studied the influence of vascular cells on patient-derived glioma stem cells. Their model further presents for development of future therapeutic strategies tailored toward disrupting key molecular pathways involved in glioma stem cell regulatory mechanisms.

David Kaplan and colleagues reported synthesis and characterization of protein-based silk-collagen composite biomaterials, with enhanced biophysical properties, for engineering of a 3D full thickness human skin system. Their tissue model system provided a suitable environment for multi-culture of cells, including neurons and immune cells, demonstrating its utility as a reliable substitute to animal models, for research on skin diseases and drug discovery.

Cherie Stabler and Edward Phelps provided important insight into *ex vivo* models related to diabetes. In general islet microphysiological systems are limited and attributed to their poor cell survival and function outside of the body. Stabler and colleagues sought to recapitulate the *in vivo* perislet niche using decellularized extracellular matrix hydrogels. Sourcing from porcine bladder, lung, and pancreas tissues, they engineered 3D hydrogels and validated using both rodent and human pancreatic islets. These supportive 3D physiometric bioadhesive hydrogels can be leveraged within microfluidic platforms for the long-term culture of islets. Phelps and colleagues, on the other hand, discuss the pathophysiology of type-1 involving microenvironments, immune cell – islet cell interactions, and the eventual breaking of immune tolerance leading to beta cell death. They review recent advances in this field and suggest ways to synergize systems to model and observe the pathophysiology of autoimmune diabetes with bioengineered therapeutic strategies.

James Hudson demonstrated the development of a culture system to engineer *ex vivo* human skeletal micro muscles (hμMs). The engineered hμMs comprised of bundles of striated and functional myofibres, which responded appropriately to electrical stimulation. They stimulated hμM to recapitulate known features of exercise training including myofibre hypertrophy and increased expression of metabolic proteins. The engineered platform enables high-throughput studies of human skeletal muscle biology and exercise physiology. On a similar line, Tony Mikos and colleagues comprehensively reviewed recent advances in the development of muscle-on-a-chip technologies for drug screening and studying muscular diseases. They reviewed current muscular disease models and the use of microfluidic platforms to understand disease pathology and high throughput screening of therapeutics for muscular myopathies.

Nenad Bursac and his team study the effect of electrical stimulation on the maturation of 3D tissue-engineered human muscles (myobundles). They showed that stimulation frequency and duration had effects on myobundle size, sarcomeric protein abundance, calcium transient amplitude, and myotube hypertrophy. In addition, electrically stimulated myobundles demonstrated a decrease in fatigue resistance and an increase in glycolytic and fatty acid metabolic flux. This platform can be

used as an advanced *in vitro* model of human skeletal muscle with improved structure, function, maturation, and metabolic flux.

In this issue, Celeste Nelson and his team reviewed the application of 3D culture models for studying branching morphogenesis of mammary glands and the mammalian lung in both normal tissue development and disease manifestation. In this review article, they summarized the limitation of 3D culture models used for understanding the mechanisms of branching in the mammary gland and mammalian lung and provided their insight on the potential future directions for engineering the next generation of 3D culture models for studying tissue morphogenesis. On the other hand, Ali Khademhosseini and his colleagues reviewed recent advances in engineering *ex vivo* vascularized tissue constructs using advanced 3D bioprinting techniques. These technologies can be used to form vascularized tissue constructs with vasculatures ranging from capillaries to large blood vessels. They discussed how these advanced technologies can be implemented for patterning proangiogenic factors to maintain the long-term, stimuli-controlled formation of new capillaries. The development of new technologies to print complex 3D vascular networks may offer an opportunity to engineer functional thick *ex vivo* tissue constructs.

It has been a pleasure and an honor to put this themed issue together. The editors would like to thank all the authors, Editor-in-Chief Kam W. Leong, and to the Elsevier team for their generous time. We believe that this collection of reviews serves not only as a testimony to the enormous promise of *ex vivo* organoids and on-chip technologies but also as a foundation for understanding the challenges and barriers for making organotypic and body-on-chip platforms. We sincerely hope that the biomaterials scientists, biomedical engineers, clinicians, and the life sciences community will find inspiration from this collection and contribute synergistic and transformative new ideas to further advance this field for fundamental biological studies and targeted drug discoveries.

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